PATENT
Docket No.: **19603/2595 (CRF D-2400)**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Hempstead et al.	Examiner: Gary B. Nickol, Ph.D.
Serial No.	:	09/830,520	
Cnfrm. No.	:	9715	Art Unit: 1642
Filed	:	October 28, 1999	
For	:	METHOD FOR REGULATING ANGIOGENESIS AND VASCULAR INTEGRITY USING TRK RECEPTOR LIGANDS	

REPLY BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. § 41.41, appellants hereby submit their reply brief.

The Examiner's Answer constitutes a continuation of the flawed pattern of analyzing the present situation. In essence, the examiner clings to isolated statements in U.S. Patent No. 5,733,871 to Alps et. al., ("Alps"), disregarding what this reference teaches as a whole and what those skilled in the art believe that it teaches. In maintaining his rejection of the claims, the examiner relies on the doctrine of inherency. However, he stretches the doctrine well beyond what is permissible in the area of methods of therapeutic treatment. Further, a careful analysis of what Alps teaches—i.e. the experimental work and the invention described in the Summary of the Invention and Detailed Description of Preferred Embodiments Sections of Alps—demonstrates that the requirements for inherency cannot be met.

As pointed out in appellants' opening brief, 35 U.S.C. §§ 100(b), 101 state that patent protection is available for new uses of known materials. The Examiner's Answer dismisses this argument as irrelevant, because no rejection has been made under 35 U.S.C. § 101. This completely misses the point. It is well settled that patent protection is available in the area of

therapeutics for new methods of treatment using known (or unpatentable) compounds. *In re Schoenwald*, 964 F.2d 1122, 22 USPQ2d 1671 (Fed. Cir. 1992) (compound not new but method of using it to treat dry eye syndrome is patentable) and *In re Shetty*, 566 F.2d 81, 195 USPQ 753 (CCPA 1977) (compound obvious but method of using it for curbing appetite is patentable). The examiner has pushed the doctrine of inherency to the point where such patent protection is no longer possible, in derogation of the Title 35 and the above precedent. To be in harmony with such authorities, the doctrine of inherency cannot expanded, as the examiner has done here, to the point that once a reference teaches administering a compound to a subject for a particular therapeutic purpose, patent protection for administering that compound for all therapeutic purposes is no longer available.

The bulk of the cases relied on in the Examiner's Answer to support the inherency position have nothing to do with the patentablity of a new therapeutic method/use. *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) relates to a zeolite molecular sieve catalyst. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971) relates to claims for a polymer-containing composition. The claimed subject matter of *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 67 USPQ2d 1664 (Fed. Cir. 2003) is a particular chemical compound which is therapeutically useful; however, the claims on appeal have nothing to do with a method directed to a new use of a compound previously known to have different therapeutic use.

Only *Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1376, 58 USPQ2d 1508, 1514 (Fed. Cir. 2001) relates to claims for methods of treatment, and there the Court expressly acknowledged that new uses of known processes may be patentable (citing 35 U.S.C. §§ 100(b), 101). However, it was held that the claimed process was not directed to a new use/method for a known compound. The *Bristol-Myers Squibb* Court went on to note that newly discovered results of known processes are not patentable under the doctrine of inherency. *Id.* However, the presently claimed invention does not pertain to newly discovered results but rather to the new use of treating a patient with cardiac ischemia or a vascular disorder by inducing angiogenesis.

As noted in appellants' opening brief, the focus of Alps is directed to the treatment of neuronal damage in the central nervous system. Indeed, a review of this reference's entire disclosure makes clear that the use of neuronal factors for such treatment is pervasively present. To overcome this, the examiner seizes on the abstract and col. 4, lines 55-58 of Alps as support for his position that Alps "teaches the intravenous administration of BDNF, NT-3,

or NT-4 for the treatment of strokes and cardiac arrests" (citations omitted). However, nowhere does Alps actually correlate the administration of these specific compounds to the treatment of strokes and cardiac arrest; the compounds are mentioned, *inter alia,* in the abstract, while col. 4, lines 55-58, in discussing strokes and cardiac arrest, does not mention these compounds. Further, when the cited sentence in column 4 is read in the context of what is set forth in the 2 sentences preceding it (as opposed to the examiner's reading in isolation), it is apparent that Alps is not actually treating stroke or cardiac arrest but rather the conditions that result from stroke or cardiac arrest—i.e. ischemic or hypoxic damage or neurodegeneration. This is also made clear by the sentence in col. 5, lines 3-6 of Alps which explicitly states "[t]he neurotrophic factors are useful for treating neuronal damage **caused by strokes** and other neurological disorders associated with generalized cell hypoxia, ischemia or neurodegeneration (emphasis added)." Also see col. 6, lines 55-62 which states:

> A multitude of diseases and disorders may cause neuronal damage, in addition to affecting other types of cells and may be treated by the compositions and methods of this invention. The following is intended to indicate **the breadth of diseases and disorders, including stroke and cardiac arrest, which cause neuronal damage** and for which the present pharmaceutical composition or the present method can be used.

(emphasis added). Thus, Alps is treating the symptom of neuronal damage rather than its cause—e.g., stroke or cardiac arrest.

The statement in the Examiner's Answer that Alps "teaches the intravenous administration of BDNF, NT-3, or NT-4 for the treatment of strokes and cardiac arrests, which as set forth previously, would inherently induce angiogenesis" is also in error, because, as noted in appellants' opening brief, Alps only teaches achievement of angiogenesis with bFGF. This is not surprising, because bFGF's ability to do so was well known. On the other hand, as also noted in the opening brief, based on the Declaration of Joseph A. Madri Under 37 C.F.R. § 1.132 ("Madri Declaration") at ¶ 10, those skilled in the art would not have regarded BDNF, NT-3, or NT-4 as being relevant to inducing angiogenesis. Indeed, in order to take the position that Alps teaches the use of such trk receptor ligands to treat cardiac ischemia or a vascular disorder, one of ordinary skill in the art would have to select BDNF, NT-3, and NT-4 from Alps' list containing other types of factors. Such a selection would be particularly unlikely, because the factors exemplified (and presumably preferred by Alps) are not BDNF, NT-3, and NT-4. Moreover, a selection of the claimed species from the Alps'

genus of neurotrophic factors amounts to an issue of obviousness (see *Eli Lilly & Co. v. Board of Regents of the University of Washington*, 334 F.3d 1264, 1270, 67 USPQ2d 1161, 1165 (Fed. Cir. 2003)), and it is well settled that the doctrine of inherency is not relevant to the question of obviousness. *See In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993); *In re Shetty*, *supra*; *In re Spormann*, 363 F.2d 444, 150 USPQ 449 (CCPA 1966).

Page 5 of the Examiner's Answer states that "the current claims and the cited art teach administering the same compound to treat the same group of patients." Appellants disagree with the correctness of this statement and, even if true (which appellants do not accept), submit that that point is not dispositive. Appellants have addressed the entirety of the Alps' disclosure and have demonstrated that it does not deal with treating the claimed conditions.

With regard to the examples, as noted in appellants' opening brief, Alps uses focal or global ischemia models to induce neuronal damages which is then treated—the models are not treated for cardiac ischemia or a vascular disorder, as claimed. Apparently, the examiner does not disagree with the inability of Alps' examples to support an inherency position, because his only response to appellant's argument regarding the examples is that those arguments are not directed to the remainder of the reference (Examiner's Answer, p. 4).

As to the Summary of the Invention and Detailed Description of Preferred Embodiments sections of Alps, for the reasons stated above, it is apparent that Alps is treating patients with neuronal damage—not stroke or cardiac arrest. Further, even if, assuming *arguendo*, the patients in Alps and the claimed invention are the same, which appellants do not agree with, these sets of patients are treated in very different ways to deal with the very different conditions being treated. In general, to avoid having therapeutics be degraded or otherwise prevented from effectively reaching their intended target as they move through the body, skilled practitioners would direct those therapeutics to where they are most needed. Indeed, Alps (col. 2, lines 23-36) says as much with regard to CNS treatment in the following passage:

> Administration of neurotrophic factors in the periphery for a site of action in the CNS presents several problems. For example, in vivo intravenous administration of neurotrophic factors subjects them to degradative processes in the body, including proteases, which can breakdown the protein prior to its desired

> action in the CNS.[1] Many charged molecules, including neurotrophic factors, bind to the extracellular matrix. Some neurotrophic factors affect non-neuronal cells, e.g., FGFs. Such activity may decrease the neurotrophic factor's ability to act on neuronal cells. In addition, the administration of drugs into the periphery for uptake into the CNS presents unique challenges because the blood-brain barrier prevents the entry of large molecules into the cerebral extracellular space and cerebral spinal fluid (CSF).

For the above reasons, those practicing Alps' invention would direct the subject neurotrophic factors to different locations than where those carrying out the present invention would direct the subject trk receptor ligands. In treating neuronal damage in accordance with Alps, the neurotrophic factors are administered to the brain in a manner suitable to treat neurons in the areas of the brain which are likely to be injured. The case of cardiac arrest (i.e. where the heart stops and blood is not supplied to the brain, thereby causing the neuronal damage that Alps treats) is not the same condition as cardiac ischemia which appellants treat. In treating cardiac ischemia in accordance with appellants' invention, the claimed trk receptor ligands would be directed to the heart—not the brain. In treating a vascular disorder in accordance with the present invention, the trk receptor ligands would be directed to the blood vessel being treated. On the other hand, where one of ordinary skill in the art is treating neuronal damage resulting from stroke, in accordance with Alps, the subject neurotrophic factor would not be directed to the occluded blood vessel but to portions of the brain susceptible to resulting damage. Thus, the present invention involves treating different patients in different ways than Alps.

The examiner's position with regard to the Madri Declaration is completely at odds with binding precedent. In his declaration, Dr. Madri, utilizing his expertise in the art, states that having reviewed Alps, it is his opinion that one of ordinary skill in the art would not regard Alps as teaching that BDNF, NT-3, or NT-4 are useful in promoting angiogenesis, particularly in a patient that has cardiac ischemia or a vascular disorder (Madri Declaration ¶¶ 4, 6, 9, 10). *Rosco, Inc. v. Mirror Lite Co.*, 304 F.3d 1373, 64 USPQ2d 1676 (Fed. Cir. 2002) demonstrates that such expert testimony regarding what is taught by a reference alleged to inherently disclose the claimed invention is highly relevant. There is no apparent

---

[1] This is not an issue with regard to delivery of nucleic acid molecules, in accordance with pending claims 18 and 59. Therefore, these claims are independently patentable of their own accord. No where does Alps teach or suggest the subject matter of these claims.

quarrel with Dr. Madri's qualifications as an expert. However, rather than presenting countervailing evidence or his own affidavit, the examiner dismisses appellants' arguments by noting that the *Rosco* case simply relates to a design patent. This is a distinction without a difference. The language from *Rosco* which is quoted in appellants' opening brief makes clear that how one of ordinary skill in the art would read a reference in an inherency situation is highly relevant. To the extent technical complexity matters, a complex technology like that of the claimed invention makes consideration of how those skilled in the art regard a reference particularly appropriate. Who better to evaluate whether a reference does or does not inherently teach what is claimed than someone skilled in the art? Here, Dr. Madri has made such an evaluation and determined that Alps is not teaching one of ordinary skill in the art that BDNF, NT-3, and NT-4 are useful in promoting angiogenesis to treat cardiac ischemia or a vascular disorder in a patient. In the absence of evidence to the contrary, this testimony should be dispositive.

For all of the reasons set forth here and in appellants' opening brief, it is clear that the rejection of the claims under 35 U.S.C. § 102(e) cannot be sustained. Accordingly, the final rejection should be reversed.

Dated: August 30, 2005

Respectfully submitted,

Michael L. Goldman
Registration No. 30,727
Attorney for Appellants

Nixon Peabody LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603-1051
Telephone: (585) 263-1304
Facsimile: (585) 263-1600

CERTIFICATE OF MAILING OR TRANSMISSION [37 CFR 1.8(a)]

I hereby certify that this correspondence is being:

☒ deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Mail Stop Appeal Brief - Patents, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450

☐ transmitted by facsimile on the date shown below to the United States Patent and Trademark Office at (703) _____.

August 30, 2005
Date

Signature

Wendy L. Barry
Type or Print Name